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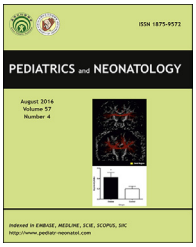

ORIGINAL ARTICLE

Predictors of Booster Response to Hepatitis B Vaccine at 15 years of age: A Cross-Sectional School-Based Study

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Key Words
adolescents;
anamnestic response;
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Background: The current consensus does not support the use of booster dose because of its anamnestic response in almost all children 15 years after universal infant hepatitis B virus (HBV) vaccination. However, in our clinical setting, numerous concerned parents request a booster administration for their children. We aimed to provide the possible predictors of booster response in adolescents before this booster administration.
Methods: This study comprised a series of cross-sectional serological surveys of HBV markers in 15-year-old individuals between 2008 and 2012. Data on serum hepatitis B surface antigen, hepatitis B surface antibody (anti-HBs), and liver-function biomarkers in a total of 887 senior high-school students were collected. There were two parts to this study: HBV seroepidemiology and booster-response analysis to identify the possible response predictors and decay factors after the HBV booster administration.
Results: The overall anti-HBs and hepatitis B surface antigen seropositivity rates were 34.7% and 0.7%, respectively, and the median anti-HBs titer was 3.3 mIU/mL. Six weeks after one dose of recombinant HBV vaccine, the overall booster-response rate in the double-seronegative recipients was 94% (471/501). Among the participants whose initial anti-HBs titers were undetectable or low, 72.4% (247/341) and 95.6% (153/160), respectively, reactivated their anti-HBs titers $\geq$ 100 mIU/mL about 6 weeks after the booster administration. The likelihood of postbooster anti-HBs titer reaching an adequate protective level increased with the prebooster titer. The female participants had stronger anamnestic responses compared to the male participants.

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Conclusion: We found that the female participants and prebooster anti-HBs titers above the detection limit of the immunoassay were good predictors of HBV booster response.

1. Introduction

The world's first nationwide hepatitis B virus (HBV) infant-vaccination program was launched in Taiwan in July 1984, starting with newborns to highly infectious mothers, and expanding to all newborns in July 1986.[1] Prior to July 1992, infants were given four doses (5 μg/dose) of plasma-derived vaccine (Hevac B; Pasteur-Mérieux, Lyon, France, or its equivalent derivative) at birth, and at 1, 2, and 12 months of age. After July 1992, three doses of recombinant vaccine [5 μg/dose of Recombivax (Merck, Merk Sharp & Dohme, Rahway, NJ, USA) or 20 μg/dose of Engerix (SmithKline Beecham, Rixensart, Belgium)] were administered before the age of 1 week, 1 month, and 6 months.[2] Based on vaccine-efficacy studies, the protective cutoff level of antibodies against the hepatitis B surface antigen (HBsAg) was set at $\geq$ 10 mIU/mL.[3] Among the children who initially responded to the primary three-dose vaccination series, 15–50% demonstrated a low or undetectable hepatitis B surface antibody (anti-HBs) level 5–15 years after primary vaccination.[4] A large-scale study provided evidence that an anamnestic anti-HBs response was absent in 10.1% of 15- to 18-year-old individuals in Taiwan, a country that had high endemicity of HBV.[5] The current guidelines from the Taiwan Advisory Committee on Immunization Practices state that individuals may receive a booster dose if they have negative anti-HBs antibodies and belong to high-risk groups (i.e., sexual/household contacts to infected people, hemodialysed, organ-transplant recipients, immunocompromised patients, intravenous drug users, participants in high-risk sexual activity, or health-care workers). Clinically, we are still encountering numerous concerned parents who request booster administrations for their children who do not belong to any high-risk group. We aimed to provide the possible predictors of booster response in adolescents before booster administration.

In this report, we describe the two parts of our study: HBV seroepidemiology and booster analysis, including immunogenicity response to booster, and the survey of the possible predictors of HBV booster response at 15 years of age.

2. Methods

2.1. Study population

This was a retrospective cross-sectional study between 2008 and 2012 composed of the serological surveys of HBV markers in newly enrolled students of the Tzu Chi senior high school (birth cohort 1993–1997) in Eastern Taiwan. A flowchart indicating our study design is depicted in Figure 1. An approval certificate for this study was issued by

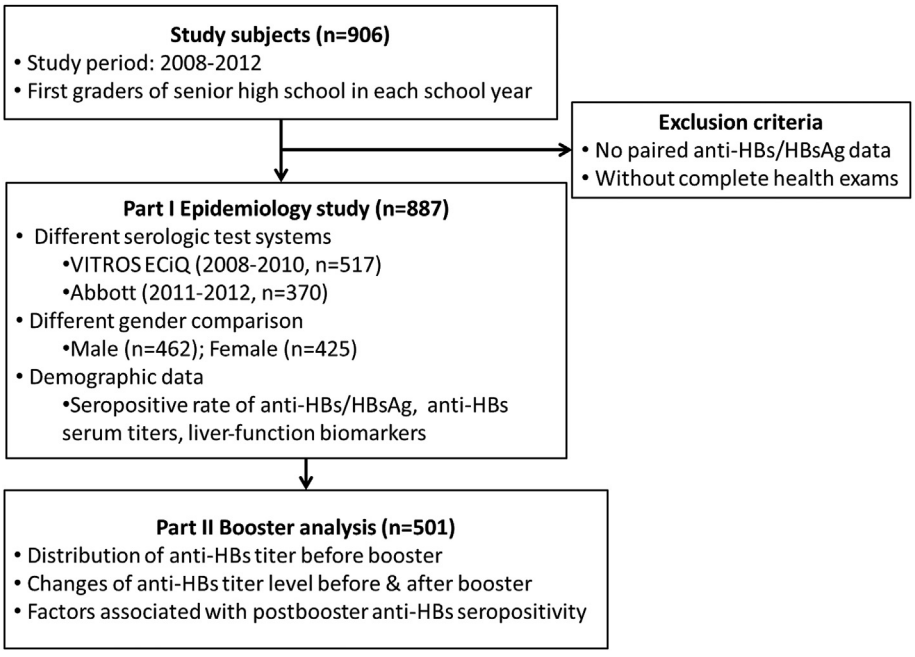

Figure 1 Flowchart of the study design. anti-HBs = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen.

the Research Ethics Committee of Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (Research Ethics Committee (REC) number: IRB101—125). A total of 906 students were initially recruited in our study, and we excluded those without the records of paired HBV markers (anti-HBs/HBsAg), as well as those without complete health examinations, leaving a total of 887 participants in the epidemiological study. The vaccination cards of each participant were not reviewed individually in our study, and the estimated coverage rates of complete HBV vaccination in our participants were comparable with the participants of the same birth cohort (1993—1997) in Taiwan. Based on the statistical data from the Center for Disease Control in Taiwan, Ni et al[6] reported that the coverage rates of complete HBV vaccination were 91.1—93.5% with birth cohort 1993—1997 in Table 1 of their study. A written consent was obtained from the students' parents or guardians upon school enrollment using forms provided by the Hualien County Government Education Bureau. The consent form informed parents/guardians that these examinations were nonintrusive with minimal risk, and the students or parents/guardians were free to withdraw from any examination parameter at any time.

2.2. Epidemiological study

Blood samples were collected from each student as a part of their health examination during the first semester of their senior high school. The rates of anti-HBs and HBsAg seropositivity, anti-HBs serum titers, and liver-function biomarkers were collected. The rates of anti-HBs and HBsAg seropositivity along with other demographic characteristics, such as sex and age and the median titers of anti-HBs, were also compared. We divided our study participants into two groups owing to the fact that different serologic test systems had been used to determine the anti-HBs titers [i.e., the VITROS ECiQ immunoassay (Ortho Clinical Diagnostics, Raritan, NJ, USA) during the school years that began between 2008 and 2010, and the Abbott Laboratories ARCHITECT (North Chicago, IL, USA) anti-HBs immunoassay during the school years that began between 2011 and 2012]. These two immunoassay systems had different detection limits. Therefore, we grouped our participants for comparison based on the assay methods used in different school years into group 2008—2010 and group 2011—2012. No data for hepatitis B core antibody were available within our database. Therefore, the prevalence rates of natural infection could not be estimated in our study.

2.3. Booster analysis

2.3.1. Response rate in booster recipients at 15 years of age

In our database, individuals demonstrating double seronegativity for anti-HBs and HBsAg were advised by the school nurses to receive one booster dose of recombinant HBV vaccine (20 μg/dose) based on the guidelines from the Taiwan Advisory Committee on Immunization Practices. If written consent was obtained from the student's parent or guardian, this booster dose was to be administered on the same day in their school clinic under the supervision of the family physician. Postbooster blood sampling for anti-HBs titers was also performed on the same day in the school clinic an average of 6 weeks after their booster date. The response rate to this single booster dose of HBV vaccine was defined as the proportion of booster recipients whose postbooster anti-HBs titer was $\geq$ 10 mIU/mL. For the evaluation of any possible predictors of booster response, a logistic-regression model was used for statistical analysis and the odds ratio (OR) was calculated. Sex and prebooster anti-HBs titers were both used as variables in our analysis.

2.3.2. Longitudinal study

After tracking our senior high-school participants by their birth cohort in our university database, we found that some of our previous booster recipients had studied in our senior high school prior to attending our university. We decided to trace the pattern of seroconversion and postbooster changes over a 3-year interval in the booster recipients from the birth cohort 1993—1994 (school year 2008—2009). We aimed to identify the factors affecting the decay rate of booster recipients by comparing the 6-week and 3-year postbooster anti-HBs titers among individuals with different prebooster titers and sex.

2.4. Serologic testing

All the quantifications of seromarkers of HBV infection were performed using enzyme immunoassays (data prior to August 31, 2011, VITROS ECiQ Immunodiagnostics System; data after September 1, 2011, Abbott Laboratories). In the VITROS system, the values of anti-HBs below 4.23 mIU/mL would be interpreted as undetectable in the school years 2008—2010. However, the value of anti-HBs below 1 mIU/mL would be interpreted as undetectable in the school years 2011—2012 by the Abbott system. The protective level of anti-HBs was defined as $\geq$ 10 mIU/mL based on the World Health Organization criteria.[3] Participants who were positive for HBsAg were assumed to be HBV carriers.[7] Elevated aspartate transaminase (AST) and alanine transaminase (ALT) were defined as $>$ 40 U/L in our study.

2.5. Statistical analysis

A Chi-square test was performed to identify the differences in anti-HBs and HBsAg seropositivity rates, and the median titers of anti-HBs between different school years, sexes, and other subgroups. Statistically significant differences were defined as $p < 0.05$. All the statistical analyses were performed using the SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA). For evaluating any possible predictors of booster response, a logistic-regression model was used for statistical analysis, and the adjusted OR was calculated.

3. Results

3.1. Part I: Epidemiological study

The study participants of this epidemiological survey consisted of 887 15-year-old individuals (462 males and 425

females), all of whom were born after 1992 within the national infant HBV vaccination era of Taiwan, and had received the recombinant HBV vaccines during their infancy. The overall anti-HBs and HBsAg seropositivity rates in our students were 34.7% and 0.7%, respectively. Table 1 shows a statistically significant difference in the seropositivity rate and median titers of anti-HBs between the different school-year groups (group 2008–2010 and group 2011–2012, $p < 0.001$). We also compared the seroprevalence of HBV markers between sexes for all participants, but there were no statistically significant differences. Elevated (> 40 U/L) AST and ALT were more prominent in male participants with statistical significance ($p = 0.022$ and $p < 0.001$, respectively), but none of the six HBV carriers in our study had elevated liver-function markers (AST and ALT).

3.2. Part II: Booster analysis

3.2.1. Distribution of prebooster anti-HBs titers in HBV booster recipients in each school year

Of these 579 individuals with double seronegativity of anti-HBs and HBsAg, 501 (86.5%) participated in this part of our booster study. We further categorized all the booster recipients based on their prebooster anti-HBs titers into an "undetectable" group, whose values were below the level of detection limit (< 4.3 mIU/mL for the 2008–2010 school years; < 1 mIU/mL for the 2011–2012 school year), and "low titer" group, whose values were between the detection limit and 10 mIU/mL. Among these 501 booster recipients, 68.1% (341/501) had prebooster anti-HBs titers that placed them in the "undetectable" group, and 31.9% (160/501) belonged to the "low titer" group.

3.2.2. Correlation of prebooster and postbooster anti-HBs titers

The 501 individuals demonstrating seronegativity for both anti-HBs and HBsAg received one booster dose of recombinant HBV vaccine (20 μg/dose). As indicated in Table 2, the distributions of prebooster and postbooster titers by sex were not significantly different. The demographic data of booster recipients show that the male individuals had higher values of AST and ALT ($p < 0.001$); furthermore, a higher proportion of individuals with elevated AST/ALT was noted among the male participants with $p < 0.030$ and $p < 0.001$, respectively. The overall response rate among booster recipients with postbooster anti-HBs titers ≥

Table 1 Demographics data ($N = 887$).

Item	Year			Sex			Total ($n = 887$)
	2008–2010 ($n = 517$)	2011–2012 ($n = 370$)	p	Male ($n = 462$)	Female ($n = 425$)	p	
Sex			0.454			NA	
Male, n (%)	275 (53.2)	187 (50.5)		462 (100.0)	0 (0.0)		462 (52.1)
Female, n (%)	242 (46.8)	183 (49.5)		0 (0.0)	425 (100.0)		425 (47.9)
Age, mean ± SD (y)	15.5 ± 0.4	15.5 ± 0.4	0.190	15.5 ± 0.4	15.5 ± 0.4	0.271	15.5 ± 0.4
Anti-HBs			<0.001*			0.364	
Anti-HBs (+), n (%, 95% CI)	214 (41.4, 37.2–45.6)	94 (25.4, 21.0–29.8)		154 (33.3, 29.0–37.6)	154 (36.2, 31.6–40.8)		308 (34.7, 31.6–37.8)
Anti-HBs (−), n (%, 95% CI)	303 (58.6, 54.4–62.8)	276 (74.6, 70.2–79.0)		308 (66.7, 62.4–71.0)	271 (63.8, 59.2–68.4)		579 (65.3, 62.2–68.4)
Anti-HBs titer, median	4.8	1.9	<0.001*	3.0	3.6	0.839	3.3
HBsAg			0.410			0.918	
HBsAg (+), n (%, 95% CI)	5 (1.0, 0.1–1.9)	1 (0.3, 0.0–0.9)		3 (0.6, 0.0–1.3)	3 (0.7, 0.0–1.5)		6 (0.7, 0.2–1.2)
HBsAg (−), n (%, 95% CI)	512 (99.0, 98.1–99.9)	369 (99.7, 99.1–100.0)		459 (99.4, 98.7–100.0)	422 (99.3, 98.5–100.0)		881 (99.3, 98.8–99.8)
TCH	150.5 ± 27.5	142.2 ± 27.0	<0.001*	143.2 ± 28.5	151.3 ± 25.9	<0.001*	147.0 ± 27.6
AST	20.5 ± 6.3	18.1 ± 9.6	<0.001*	21.4 ± 9.9	17.3 ± 4.0	<0.001*	19.5 ± 7.9
AST			0.912			0.022*	
≤ 40, n (%)	511 (98.8)	366 (98.9)		453 (98.1)	424 (99.8)		877 (98.9)
> 40, n (%)	6 (1.2)	4 (1.1)		9 (1.9)	1 (0.2)		10 (1.1)
ALT	16.3 ± 12.7	17.9 ± 12.4	0.074	20.6 ± 15.8	13.0 ± 5.4	<0.001*	17.0 ± 12.6
ALT			0.772			<0.001*	
≤ 40, n (%)	498 (96.3)	355 (95.9)		430 (93.1)	423 (99.5)		853 (96.2)
> 40, n (%)	19 (3.7)	15 (4.1)		32 (6.9)	2 (0.5)		34 (3.8)

Data are presented as mean ± standard deviation, or n and percentage.
*A value of $p < 0.05$ was considered statistically significant after the test.
ALT = alanine transaminase; anti-HBs = hepatitis B surface antibody; AST = aspartate transaminase; CI = confidence interval; HBsAg = hepatitis B surface antigen; NA = not available; SD = standard deviation; TCH = total cholesterol.

Table 2 Comparison between men and women among booster recipients ($N = 501$).

Item	Male	Female	Total	p
N	255	246	501	NA
Age, mean ± SD (y)	15.5 ± 0.3	15.5 ± 0.4	15.5 ± 0.4	0.175
Prebooster anti-HBs	—	—	—	0.495
Undetectable	170 (66.7)	171 (69.5)	341 (68.1)	
Low titer	85 (33.3)	75 (30.5)	160 (31.9)	
Median titer (IQR)	1.4 (2.81)	0.8 (2.95)	1 (2.91)	0.246
Postbooster anti-HBs	—	—	—	0.122
<10	20 (7.8)	10 (4.1)	30 (6.0)	
10—99	41 (16.1)	30 (12.2)	71 (14.2)	
100—999	109 (42.7)	108 (43.9)	217 (43.3)	
≥1000	85 (33.3)	98 (39.8)	183 (36.5)	
Median titer (IQR)	558.6 (891.0)	673.5 (808.5)	570 (851.5)	0.066
TCH	144.4 ± 27.5	150.3 ± 25.4	147.3 ± 26.6	0.013*
AST	21.3 ± 7.8	17.0 ± 3.6	19.2 ± 6.5	<0.001*
AST	—	—	—	0.030*
≤40, n (%)	249 (97.6)	246 (100.0)	495 (98.8)	
>40, n (%)	6 (2.4)	0 (0.0)	6 (1.2)	
ALT	22.0 ± 17.6	13.1 ± 4.7	17.6 ± 13.7	<0.001*
ALT	—	—	—	<0.001*
≤40, n (%)	231 (90.6)	246 (100.0)	477 (95.2)	
>40, n (%)	24 (9.4)	0 (0.0)	24 (4.8)	

Data are presented as mean ± standard deviation, or n and percentage.
*A value of $p < 0.05$ was considered statistically significant after the test.
ALT = alanine transaminase; anti-HBs = hepatitis B surface antibody; AST = aspartate transaminase; IQR = interquartile range 25—75%; NA = not available; SD = standard deviation; TCH = total cholesterol.

10 mIU/mL was 94% (471/501) at 6 weeks after booster administration. The median anti-HBs titers in recipients before and after booster administration were 1 mIU/mL (IQR 2.91) and 570 mIU/mL (IQR 851.5), respectively. IQR stands for the "interquartile range." We also observed a statistical trend in female individuals who had higher median titers of anti-HBs after booster administration ($p = 0.066$).

In Figure 2, the bubble plot shows the change in anti-HBs titer level before and after the HBV booster administration. Among the 341 participants in the "undetectable" group, 44.6% (152/341) attained postbooster titers ranging from 100 mIU/mL to < 1000 mIU/mL, and 27.9% (95/341) had postbooster titers ≥ 1000 mIU/mL. For these 160 participants in the "low titer" group, 40.6% (65/160) had the postbooster titers ranging from 100 mIU/mL to < 1000 mIU/mL, and 55% (88/160) had postbooster titers ≥ 1000 mIU/mL. All 6% (30/501) of the recipients who failed to reactivate their immune memory belonged to the "undetectable" group before the booster dose.

In Table 3, the comparison between sexes shows that, compared to the male participants, the female participants had a higher likelihood, as indicated by the adjusted multivariate OR 2.04 [95% CI 0.92—4.52], of achieving postbooster anti-HBs titers ≥ 10 mIU/mL; if the target value of postbooster titers was set as ≥ 100 mIU/mL, the adjusted OR of female participants became 1.72 (95% CI 1.08—2.73). When the prebooster titer was used as variant for the logistic-regression analysis, the "low titer" group was more likely to achieve a target anti-HBs titer ≥ 100 mIU/mL compared to the "undetectable" group, as reflected by the adjusted multivariate OR 7.51 (95% CI 3.34—16.91).

3.2.3. Longitudinal study

In our previous study in 2014,[8] we studied 38 18-year-old individuals (birth cohort 1993—1994) who had studied in our senior high school prior to attending our university. Among the 25 booster recipients, 96% (24/25) regained protective levels of anti-HBs with a median anti-HBs titer of 353 mIU/mL after one booster dose of HBV vaccine at age 15. However, among the 24 recipients who were anti-HBs seropositive at 6 weeks after booster administration, seven individuals (29.2%) had lost their anti-HBs seropositivity again within 3 years. During this interval, the median anti-HBs titer decayed from 353.0 mIU/mL to 21.1 mIU/mL (94% reduction). The percentages of decay rate among female and male individuals within a 3-year interval were 89.2 ± 12.2 and 76.0 ± 28.9, respectively ($p = 0.159$). The percentages of decay rate among the "undetectable" and "low titer" groups were 82.5 ± 24.1 and 83.5 ± 10.3, respectively ($p = 0.942$), as shown in Table S1. There were no statistically significant differences due to the small sample size in this longitudinal study.

4. Discussion

In previous studies conducted in Taiwan, the anti-HBs seropositivity rate declined from 99% at 1 year of age to 83% at 5 years of age,[9] and further dropped to 37% at 15—17 years of age.[10] In a 2004 survey, Ni et al[6] showed that the anti-hepatitis B core seropositivity rate was low (1%) in children less than 15 years of age. In the report by Lin et al,[11] the age of the participants was very close to the one in this study (16 and 15.5 years); the anti-HBs and HBsAg

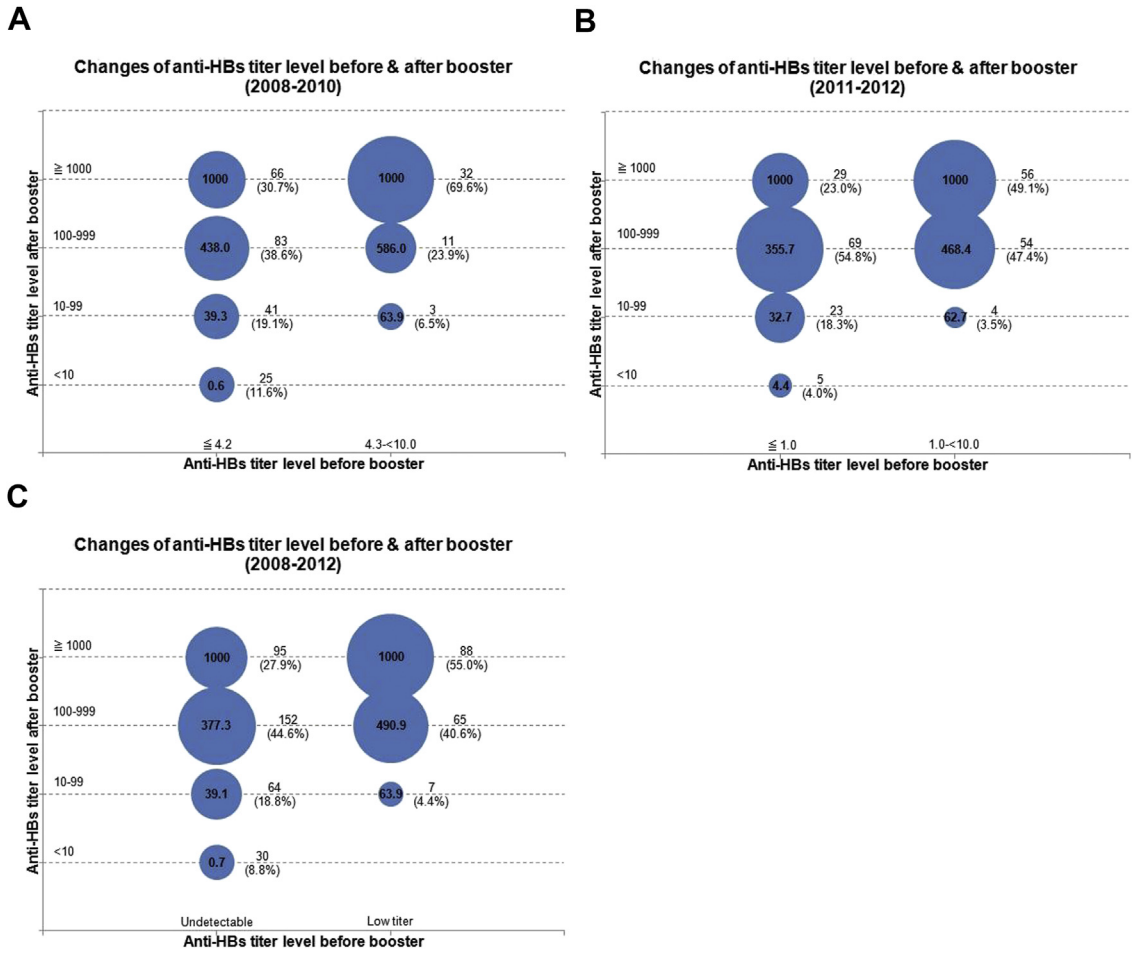

Figure 2 Change in hepatitis B surface antibody titer level before and after the hepatitis B virus booster administration. anti-HBs = hepatitis B surface antibody.

seropositivity rates in their recombinant group were 34% (448/679) and 0.7% (5/679), which were comparable with the seropositivity rates of anti-HBs (34.7%) and HBsAg (0.7%) in our study.

Based on data from previous studies, different types of hepatitis B vaccines, doses, and brands, as well as the timing of primary vaccination, can all influence the persistence of anti-HBs titers.[12] Therefore, only those who

Table 3 Logistic-regression analysis for factors associated with booster response by different postbooster hepatitis B surface antibody titer ($N = 501$).

	Postbooster anti-HBs titer > 10				Postbooster anti-HBs titer > 100			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Sex	—	—	—	—	—	—	—	—
Male	1	NA	1	NA	1	NA	1	NA
Female	2.01 (0.92—4.38)	0.080	2.04 (0.92—4.52)	0.080	1.62 (1.04—2.53)	0.034*	1.72 (1.08—2.73)	0.023*
Period	—	—	—	—	—	—	—	—
2008—2010	1	NA	1	NA	1	NA	1	NA
2011—2012	4.98 (1.87—13.23)	<0.001*	3.05 (1.13—8.22)	0.027*	2.34 (1.47—3.71)	<0.001*	1.53 (0.94—2.50)	0.089
Prebooster anti-HBs titer	—	—	—	—	—	—	—	—
Undetectable	1	NA	1	NA	1	NA	1	NA
Low titer	1.56E8 (NA)	0.995	1.09E8 (NA)	0.995	8.32 (3.76—18.40)	<0.001*	7.51 (3.34—16.91)	<0.001*

Data are presented as odds ratio (95% CI).
*A value of $p < 0.05$ was considered statistically significant after the test.
anti-HBs = hepatitis B surface antibody; OR = odds ratio; CI = confidence interval; NA = not available.

received recombinant HBV vaccine were selected in our study to avoid the possible interference of different vaccine types given in infancy. Our results found that the participants in 2008—2010 had higher seropositive rates of anti-HBs and median anti-HBs titers than those of 2011—2012 (41.4% vs. 25.4%, $p < 0.001$). However, individual vaccination cards and background information, such as household contact, were not provided in our database, so further study should be conducted to identify the possible reasons of this significant difference. Nevertheless, there were no statistically significant differences of seropositive rate of HBV markers between sexes for all participants in this study.

Among the 501 individuals who were our booster recipients, the booster-response rate was 94% (471/501) after one booster dose of recombinant HBV vaccine (20 μg/dose), which demonstrated the integrity of anamnestic response in our 15-year-old recipients. Lin et al[11] showed that the booster-response rate to one dose of recombinant HBV vaccine was 95.9% (326/340) in 16-year-old participants who received recombinant HBV vaccine during their neonatal immunization.

Jan et al[13] showed that, when immune memory was present, the anti-HBs responses could be induced as early as 1 week following a booster, and such responders were likely to have protective titers after a single dose. In their study, almost all early responders (anti-HBs $\geq$ 10 mIU/mL at 7—10 days after a booster dose) had high anti-HBs titers ($\geq$ 100 mIU/mL) after 1 month.[13] Defining the presence of HBV vaccine immune memory could be problematic, because the production of anti-HBs titers $\geq$ 10 mIU/mL 1 month after booster vaccination may result from either a primary immune response or anamnestic response. Therefore, the group of individuals who mounted low-level anti-HBs (10—99 mIU/mL) responses after one dose of HBV vaccine may have manifested an anamnestic response or a primary response after the loss of immune memory.[13]

As illustrated in Figure 2, our study showed that 72.5% (247/341) of the participants in the "undetectable" group reactivated their anti-HBs titers to $\geq$ 100 mIU/mL about 6 weeks after one booster dose of HBV vaccine. In the "low titer" group, 95.6% of the participants regained postbooster titers of anti-HBs above 100 mIU/mL within the same time interval. The likelihood of postbooster titer reaching an adequate protective level increased with the prebooster anti-HBs titers, up to postbooster anti-HBs titers as high as $\geq$ 100 mIU/mL.

Sex difference was another factor found to affect the booster response in our study. We found that the female participants had a significantly stronger booster response compared with the male individuals (adjusted OR 1.72). It was previously reported that, in humans, female individuals usually express higher levels of antibodies and antibody-stimulating Th2 cytokines.[14,15] Females also had a stronger immunogenic response to HBV vaccine with higher anti-HBs seropositivity and a reduced chance for hepatitis B infection.[16—18] However, we did not detect significant sex differences in anti-HBs titers and HBsAg seropositivity rates in this study, although we did observe a greater proportion of male individuals with elevated AST/ALT. In this study, the female individuals seem to correlate with a trend of faster anti-HBs decay.

In conclusion, we found that 91.2% of those recipients in the "undetectable" group were able to reactivate their immune memory to achieve protective anti-HBs titers after one booster dose of HBV vaccine. The likelihood of postbooster titer reaching an adequate protective level increased with the prebooster anti-HBs titers. Female individuals had stronger anamnestic response than male individuals.

There were major limitations to our study. First, this retrospective cross-sectional study, including the design and records analysis, was conducted without reviewing the vaccination records of the participants. Second, we could not verify whether the participants had HBV booster vaccinations prior to our booster study. Third, the types of recombinant HBV vaccine (e.g., 5 μg/dose of Recombivax or 20 μg/dose of Engerix) used for the neonatal immunization of each booster recipient could not be identified; therefore, the possible dosage effects of HBV vaccine on our booster response could not be evaluated.

Conflicts of interest

The authors declare that they have no competing interests.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.pedneo.2015.09.006.